REMARKS

Applicants have amended the title to more specifically describe the invention. Submitted herewith is a response to the Notice to Comply, which amends the specification to include a copy of the sequence listing.

Claims 1-13 are pending in the application. Applicants have cancelled Claims 1-3 and 9-10 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 4 to be in independent form, and have amended Claims 5 and 12 to depend from Claim 4. Claim 13 is amended to replace the term "epitope tag" with the term "tag polypeptide." Applicants have amended Claims 4 and 5 to specify "wherein said isolated polypeptide is more highly expressed in normal esophagus tissue compared to esophageal tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophagus tissue compared to esophageal tumor." Claims 4-6 have been amended to delete elements (c) and (d). New Claims 14-17 have been added. Claims 4-17 are presented for further examination.

Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendments to Claim 13 can be found, for example, at paragraph [0229]. Support for the amendments to Claims 4 and 5 can be found, for example, in Example 18, beginning at paragraph [0529] as well as paragraph [0336] of the specification. Support for the amendments to Claims 4-6 and 9-10 can be found, for example, at Figure 136 of the specification. Support for new Claims 14-17 can be found, for example, in the claims as originally filed and paragraphs [0336], [0362], [407], and Example 18 starting at paragraph [0529].

Claims 4-17 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed January 11, 2005. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 C.F.R. § 1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in 37 C.F.R. § 1.17(i) is submitted herewith.

Specification

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO maintains that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a separate part of the disclosure on a paper copy, a Sequence Listing as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a copy of the Notice to Comply and a response which a mends the specification to include a paper copy of the Sequence Listing, which is also submitted herewith.

Information Disclosure Statement

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement filed September 17, 2002. Applicants submit herewith more detailed information regarding the publication date of the cited sequences (Exhibit 1).

Priority Determination

The PTO has stated that because the claimed polypeptide has no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 7, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 4, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed

12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/170262 filed 12/9/1999.

Applicants submit that for the reasons stated below, the claimed polypeptides have a credible, substantial, and specific utility. The sequence of SEQ ID NO: 136 was first disclosed in US Provisional Application 60/170262 filed 12/9/1999 in Figure 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-13 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "the extracellular domain" as PRO1926 is not disclosed as being expressed on a cell surface. The PTO further objects to the recitation of "the extracellular domain", "lacking its associated signal sequence" because a signal sequence is not generally considered part of an extracellular domain.

Applicants have canceled Claims 9-10 and have amended Claims 4-6 to delete elements (c) and (d), thereby obviating the PTO's rejection based on the recitation of "the extracellular domain." Accordingly, Applicants request that the PTO reconsider and withdraw the indefiniteness rejection under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 101 – Utility

The PTO has rejected Claims 1-13 as lacking a specific, substantial, and credible utility. The PTO maintains that the classification of PRO1926 as a transmembrane polypeptide, and the identification of N-glycosylation sites, glycosaminoglycan attachment sites, cAMP and cGMP-dependent protein kinase phosphorylation sites, N-myristolylation sites, amidation sites and ATP/GTP binding motifs do not confer utility on the claimed polypeptides. According to the PTO, there is no functional characteristic associated with these motifs or domains, and their existence is not probative of function or utility.

The PTO also asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1926. One of the asserted utilities for the claimed polypeptides is use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1926 cDNA is more highly expressed in normal esophagus tissue compared to esophageal tumor. The PTO asserts that the evidence that the polynucleotide is more highly expressed in normal esophagus tissue is insufficient because it does not disclose the biological significance of the high or low expression level, nor the correlation between the high/low expression of the DNA encoding protein PRO1926 and a predisposition to the onset of esophageal tumors, i.e., whether it is the cause or result of the tumors. Further, the PTO argues that there is no supporting evidence to indicate that the encoded polypeptide has higher lower expression in tumor tissue compared to their normal tissue counterparts. The PTO also asserts that the evidence is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to esophageal tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. The PTO asserts that without knowing the identity of the tumor, one of skill in the art cannot use the protein or antibodies for diagnostic or therapeutic purposes.

The PTO states that the specification does not disclose a correlation between any specific disorder and the altered level or form of the claimed polypeptides. The PTO also states that because cancerous tissue is aneuploid, the data is unreliable. Finally the PTO argues that there is no necessary correlation between protein expression and nucleic acid levels.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. " Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the

art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill**

in the art would be convinced, to a reasonable probability, that the asserted utility is true. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

*The Data in Example 18 are Data Regarding Differential mRNA Levels, **not** Gene Amplification*

Applicants begin by clarifying that the data concerning the differential expression of the PRO1926 gene presented in Example 18 relate to gene expression, **not** gene amplification. The description of Example 18 makes clear that the results were obtained by quantitative PCR amplification of cDNA libraries. It is well known in the art that cDNA libraries are made from mRNA, and reflect the level of mRNA for a particular gene in the source tissue. Thus, Example 18 is reporting a measure of the *expression* of the PRO1926 gene, i.e. mRNA levels, not its *amplification*, i.e. the number of copies of PRO1926 in the genome.

As the PTO has indicated, gene amplification, i.e. an increased number of copies of a gene in the genome, can result from tissue being aneuploid. The PTO states that Sen *et al.* teaches that cancerous tissue is known to be aneuploid, and that higher amplification of a gene does not necessarily mean higher expression in the cancerous tissue. The PTO suggests that the results reported in Example 18 are unreliable because they "are not corrected for aneuploidy." Office Action at 7. The PTO also relies on Pennica *et al.* to teach that "it does not necessarily follow that an increase in gene copy number results in increased gene expression." Office Action at 8 (emphasis added).

Whether or not gene amplification leads to increased gene expression is irrelevant to this particular application. Likewise, whether the differential mRNA expression of the PRO1926 gene reported in Example 18 is due to an increase or decrease in copy number, or alternatively

due to an increase or decrease in transcription rates is simply not relevant. Applicants have provided reliable evidence that the PRO1926 mRNA is differentially expressed in esophageal tumor compared to normal esophageal tissue. Whether this differential expression is due to changes in gene copy number, transcription rates, a combination of the two, or some other known or unknown cellular mechanism is simply not relevant to Applicants' asserted utility. It is not clear how Applicants should "correct" the reported results for aneuploidy.

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly melanoma. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1926 polypeptide is more highly expressed in normal esophageal tissue compared to esophageal tumor;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1926 polypeptide is decreased in esophageal tumors compared to normal esophagus tissue, it is likely that the expression of PRO1926 polypeptide in esophageal tumors is also reduced, and it is therefore useful as a diagnostic tool.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding the biological significance of the differential expression, or whether it is the cause or result of the tumors;

2. The PTO cites Sen *et al.* and Pennica *et al.* to support its position that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression;

3. The PTO concludes that based on the cited literature, the data of Example 18 do not necessarily indicate anything significant regarding the claimed polypeptides. Therefore, further research needs to be done to use PRO1926 as a diagnostic tool for esophageal tumors. *See* Office Action at 6-9.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, (attached as Exhibit 2) which establishes the reliability of the data of Example 18. Knowing the biological significance of the data, or the role of PRO1926 in esophageal tumors, is not necessary to use the claimed polypeptides as cancer diagnostic tools. Second, as discussed above and can be seen from Applicants' summary of their argument, Applicants submit that any lack of correlation between gene amplification and gene expression is not at issue in this application and therefore the Sen *et al.* and Pennica *et al.* references are not relevant. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.**

Applicants have established that the Gene Encoding the PRO1926 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO1926 polypeptide in normal esophagus tissue compared to esophageal tumor is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to esophageal tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. Applicants also address the PTO's argument that because the role of PRO1926 in esophageal tumor is not known, the asserted utility is not substantial. Applicants submit that the gene

expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed polypeptides.

Applicants have submitted herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (Exhibit 2). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues.

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that a lack of known role for PRO1926 in cancer does not prevent its use as a diagnostic tool for cancer. Whether the differential expression of PRO1926 is a cause or result of the esophageal tumors is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1926 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially

expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not in normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides. (*See, e.g.,* U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 3 and 4.)

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, "a higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 7. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, as discussed above, Applicants fail to see how whether the differential expression reported in Example 18 is due to aneuploidy or not is relevant to the utility of the disclosed nucleic acids, or their corresponding polypeptides and antibodies. Regardless of whether the differential expression of the gene encoding PRO1926 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal esophagus tissue compared to esophageal tumor, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the Grimaldi Declaration submitted as Exhibit 2, establish that there is at least a two-fold difference in PRO1926 cDNA between normal esophagus tissue and esophageal tumor. Therefore, it follows that expression levels of the PRO1926 gene can be used to distinguish esophageal tumor tissue from normal esophagus tissue. The PTO has not offered any significant arguments or evidence to the contrary.

As Applicants explain below, it is more likely than not that the PRO1926 polypeptide is also differentially expressed in esophageal tumor tissue, and can therefore also be used to

distinguish esophageal tumor tissue from normal esophagus tissue. This provides utility for the claimed polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues that there is no supporting evidence that the polypeptide encoded by the nucleotide of the instant invention is more highly expressed in the normal tissue compared to the tumor tissue. The PTO also states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression.

Relying on a single example of one gene reported in Pennica, the PTO states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 8-9. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, as Applicants have stated above, **whether an increase in gene copy number leads to an increase in gene expression or protein expression is not presently an issue in this application.** The data of Example 18 reflects mRNA data as assessed by examining cDNA created from mRNA. It is not gene amplification data. Thus, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. **It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels.** The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO1926 in normal esophagus

tissue compared to esophageal tumor. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that changes in the level of mRNA are positively correlated to the changes in the level of protein.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 5). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 6), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 7) and (4th ed. 2002) (submitted herewith as Exhibit 8)). Figure 9-2 of Exhibit 7 shows the steps at which eucarotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 7 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 7 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 7 at 453 (emphasis added). Thus, as established in Exhibit 7, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 8, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 8 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 8 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 8 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 8 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 9) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 10. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 10 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 10 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 10 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 11, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the

encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1926 mRNA is expressed at a higher level in normal esophagus tissue compared to esophageal tumor, the PRO1926 polypeptide will also be expressed at a higher level in normal esophagus tissue compared to esophageal tumor. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed polypeptides as a cancer diagnostic tool.

The Claimed Polypeptide would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between changes in gene expression and changes in protein expression for PRO1926, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the second Grimaldi Declaration, Exhibit 5, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 12), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 13). The article teaches that the HER-2/neu gene has been shown

to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal

evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in esophageal tumors and that the claimed polypeptides can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly esophageal cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertions that there is no biological activity, expression pattern, phenotype, disease of condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1926. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1926 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene encoding the PRO1926 polypeptide is more highly expressed in normal esophagus tissue compared to esophageal tumor. These data are strong evidence that the PRO1926 polypeptide is associated with esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1926 polypeptide with a specific disease. Use of the claimed polypeptides as a diagnostic tool for cancer, particularly esophageal tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1926 gene in esophageal tumor is not reliable and does not establish a correlation between the differential expression and esophageal tumors, and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed polypeptides cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the at least two-fold difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools. Applicants have demonstrated that it is not necessary to know the cause or consequence of the differential expression of PRO1926 nucleic acids and polypeptides in esophageal tumors in order to use them as diagnostic tools for cancer.

Next, Applicants submit that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reasoning or evidence to the contrary. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO1926 gene and polypeptide are differentially expressed in esophageal tumors compared to normal esophagus tissue. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is <u>not</u> required. Rather, a specific, substantial, and credible utility requires <u>only</u> a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides relating to PRO1926 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

The PTO has also stated that even if the specification taught how to use the PRO1926 polypeptide, enablement would not be commensurate in scope with Claims 1-6, 9, 10, 12 and 13, which encompass % variants of SEQ ID NO: 136, and a fragment of the extracellular domain of SEQ ID NO: 136. The PTO argues that since the biological function of PRO1926 is not clear, the skilled artisan would not be able to make PRO1926 variants or fragments comprising the sequence, and test them for biological activity. The PTO states that furthermore, the specification provides no guidance as to how the skilled artisan could use inactive PRO1926

variants or fragments, as there is no functional limitation associated with PRO1926 variants or fragments comprising the sequence in the claims. *See* Office Action at 10.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 136, and which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal esophagus tissue compared to esophageal tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophagus tissue compared to esophageal tumor" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 136 in esophagus tissue samples."

Applicants submit that the claimed polypeptides are enabled, as one of skill in the art would know how to make and use them. Applicants submit that it is well-established in the art how to make polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 136. Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in esophageal tumors compared to normal esophagus tissue. Applicants have also disclosed how to make antibodies to the polypeptide of SEQ ID NO: 136, and given the high amino acid sequence homology of the claimed polypeptides, one of skill in the art would know how to make antibodies to SEQ ID NO: 136 from the claimed polypeptides. Thus, one of skill in the art would know how to make the claimed polypeptides.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO1926 gene and polypeptide are differentially expressed in esophageal tumors such that they can be used as cancer diagnostic tools. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed polypeptides as diagnostic tools. For example, polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and are "more highly expressed in normal esophagus tissue compared to esophageal tumor..." can be used as diagnostic tools since the claimed polypeptides or their encoding nucleic acids are differentially expressed in esophageal tumors. Other claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and "said isolated

polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 136 in esophagus tissue samples," are also useful diagnostic tools. Because the polypeptide of SEQ ID NO: 136 is most likely differentially expressed in esophageal tumors, antibodies for specific detection of this polypeptide in esophagus tissue samples are useful diagnostic tools.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, first paragraph – Written Description

The PTO has rejected Claims 1-6, 9, 10, 12 and 13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polypeptides possess any particular biological activity, particular conserved structure, or other disclosed distinguishing feature, the claims fail the written description requirement. The PTO states that because the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, conception is not achieved until reduction to practice has occurred. Finally, the PTO states that the only factor present in the claim is a partial structure in the form of a recitation of percent identity. The PTO concludes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g.,*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 136, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal esophagus tissue compared to esophageal tumor, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophagus tissue compared to esophageal tumor" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 136 in esophagus tissue samples."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO: 136. Applicants note that the pending Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the

pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in esophageal tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 136 in esophagus tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in esophageal tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO: 136 in esophagus tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No: 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 14-19.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 136, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection Under 35 U.S.C. § 102(b)

The PTO has rejected Claims 1-13 as anticipated under 35 U.S.C. § 102(b) by Valenzuela *et al.* (WO 00/55375) (hereinafter Valenzuela), which was published September 21, 2000. The PTO maintains that Valenzuela discloses an amino acid sequence that has 100% identity to SEQ ID NO: 136 of the instant invention, and therefore anticipates Claims 1-11. The PTO also maintains that Valenzuela discloses fusion proteins and epitope-tagged proteins, and therefore anticipates Claims 12-13.

Applicants respectfully traverse.

To be anticipated under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Applicants submit that Valenzuela does not anticipate any of the pending claims because it was not published more than one year prior to the date of the instant application for patent in the United States. The instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/170262 filed 12/9/1999.

Applicants submit that for the reasons stated above, the claimed polypeptides have a credible, substantial, and specific utility. The sequence of SEQ ID NO: 136 was first disclosed in US Provisional Application 60/170262 filed 12/9/1999 in Figure 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Valenzuela was published September 21, 2001. Thus, Valenzuela was not published more than one year prior to the filing of either PCT Application PCT/US00/23328 filed August 24, 2000, or US Provisional Application 60/170262 filed December 9, 1999. The instant application claims priority to both, and therefore Valenzuela cannot be cited as prior art against the instant application under 35 U.S.C. § 102(b).

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 7, 2005

By: _____
AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

1519400_1
032805